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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/032,972 02/26/98 KROTZ

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EXAMINER

CRANE, L

ART UNIT

PAPER NUMBER

1623

DATE MAILED:

04/04/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/032,972

Applicant(s)

Krotz et al.

Examiner

L. E. Crane

Group/Art Unit

1623

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE -----3---MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 03/26/01 (RCE filing) -----

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-41 ----- is/are pending in the application.

Of the above claim(s) ----- is/are withdrawn from consideration.

☐ Claim(s) ----- is/are allowed.

☒ Claim(s) 1-41 ----- is/are rejected.

☐ Claim(s) ----- is/are objected to.

☐ Claim(s) ----- are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 - ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.
 - ☐ received in Application No. (Series Code/Serial Number) _____.
 - ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Attachment(s)

- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ ☐ Interview Summary, PTO-413
- ☒ Notice of Reference(s) Cited, PTO-892 ☐ Notice of Informal Patent Application, PTO-152
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948 ☐ Other _____

Office Action Summary

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The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1600, Art Unit 1623.

5 A Request for Continued Examination (RCE) petition has been received as of March 26, 2001 and entered. The amendment directed to claims **1 and 21** originally submitted as paper no. 17 after final has been entered and no other claims have been cancelled or otherwise amended.

10 Claims **1-41** remain in the case.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

15 "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made."

20 Claims **1-41** are rejected under 35 U.S.C. §103(a) as being unpatentable over **Ravikumar '621** (PTO-892 ref. **A**) in view of **Caruthers et al. '679** (PTO-892 ref. **G**) and further in view of **Froehler et al. '076** (PTO-892 ref. **H**) and further in view of **Sproat et al.(I)** (PTO-892 ref. **W**), **Conway et al.** (PTO-892 ref. **Y**), **Atkinson et al.** (PTO-892 ref. **Z**), and **Sproat et al.(II)** (PTO-892 ref. **RA**).

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The instant claims are directed to entirely conventional, 7 step oligonucleotide syntheses conducted using an automated device to execute steps 2-6 (aka steps b) through f)), wherein the only variation from the prior art is the choice of solvent or solvent mixture present for deprotection step (c).

Ravikumar '621 (PTO-892 ref. A) discloses entirely conventional oligonucleotide synthesis wherein the solvent for the coupling step is acetonitrile in the examples and the P-protecting group varies from the conventional phosphorus-ester protecting group. At column 3 this reference refers to several different patents which disclose the solid phase synthesis of oligonucleotides including three Caruthers et al. patents now cited herein as PTO-892 references **I, J and K**. Each of these Caruthers et al. patents discloses the automation of the synthesis of oligonucleotides via process steps closely analogous to, if not identical with, the process steps claimed herein, the most detailed disclosure occurring in Caruthers et al. '418 (PTO-892 ref. K). In the Ravikumar '621 patent at column 10, lines 1-16, a generic disclosure of the process steps leading to an oligonucleotide is presented, including acid-mediated deprotection of the 5'-hydroxyl moiety of a solid-support-attached nucleoside. However, no disclosure of any preferred solvent for the required acid reagent is included. In the same column at line 50, the removal of 5'-hydroxyl protection by contact with acid from a solid-support-attached oligonucleotide is also taught without specifying any particular solvent. At column 14, lines 5-28, a more complete disclosure of possible 5'-hydroxyl protecting groups is provided along with a list of acids effect to deprotect, but no preferred solvents are listed. At column 18, lines 37-41,

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deprotection is accomplished by contact with a solution of dichloroacetic acid in dichloromethane, conditions repeated in subsequent experimental procedures. The choice of any particular deprotection solvent is therefore apparently a choice within the purview of the ordinary practitioner in view of this disclosure. This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Caruthers et al. '679 (PTO-892 ref. G) at column 5, lines 10-14, teaches the use of "... any solvent which will dissolve the reactants ..." including a list of specific organic solvents for phosphoramidite-intermediate-based oligonucleotide synthesis. The context of this statement suggests that Caruthers was making reference to the coupling step. However, the same generic teaching appears to also apply to the deprotection step where four different solvent/reagent systems were disclosed by Caruthers as effective in the 5'-O-detritylation process:

(1) see column 16, Table IV, footnote 1 (ZnBr₂ in nitromethane);

(2) see column 16, Table V, footnote 1 (toluenesulfonic acid in chloroform:methanol (7:3));

(3) see column 18, lines 26-28 (ZnBr₂ in nitromethane:methanol (19:1)); and

(4) see column 19, lines 47-50 (80% acetic acid).

This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Froehler et al. '076 (PTO-892 ref. H) discloses the use of H-phosphonate intermediates for the coupling step in the synthesis of oligonucleotides and phosphorothioate analogues thereof, including reference to the automated synthesis thereof using a "Biosearch

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Model 8600 DNA synthesizer" at column 9, lines 22-23. This reference also teaches the use of " ... an anhydrous organic solvent, preferably pyridine/acetonitrile ...," at column 5, lines 26-28. This "what ever works best" philosophy apparently also applies to the deprotection step; see column 5, lines 38-47. The last line of this portion of column 5 is particularly instructive. After listing 3 (three) different deprotection reagent/solvent mixtures, Froehler suggests a very flexible "whatever works" approach by further stating that "[o]ther deprotection procedures suitable for other known protecting groups will be apparent to the ordinary practitioner." This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Sproat et al.(I) (PTO-892 ref. **W**) discloses at p. 52, (lines 2 and 18) that toluene is useful for the purification of synthetic nucleoside intermediates. Additionally, this reference discloses at pp. 64 (Protocol 17, step 3) and page 70 (Protocol 25, step 4) that benzene is a solvent for key oligonucleotide synthesis reagents and for nucleoside-3'-O-phosphoramidites, and may be used to co-evaporate triethylamine therefrom.

Conway et al. (PTO-892 ref. **Y**) is directed to the chemical synthesis of labeled DNA and at p. 218, Section C, Subsection 2, discloses the specific use of toluene as an effective solvent for dissolution of pyridine-contaminated dinucleoside monophosphorothioate d[Cp(s)C] prior to co-evaporative removal of the pyridine/toluene mixture therefrom. The instant reference does not disclose that toluene is used in the coupling step required to make this compound.

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Atkinson et al. (PTO-892 ref. Z) discloses at p. 43 in section (xvii), that toluene is useful to dissolve the 3'-O-phosphoramidites of 2'-deoxyadenosine, 2'-deoxycytidine, and 2'-deoxyuridine as the first step in a re-precipitation or recrystallization process. This reference also teaches at p. 76, section 7.5, "Variation in Procedures," although no specific teaching of the substitution of an aromatic solvent from other solvents used in oligonucleotide synthesis is present in this section. In section 8.7 at p. 80, "toluene" is listed as a reagent useful in the preparation of "Deoxyribonucleoside-derivatized supports." This reference at the noted locations does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

Sproat et al.(II) (PTO-892 ref. RA).at p. 84, lines 10 and 9 from the end of the page, discloses that the "[p]urity of solvents and reagents is of the utmost importance as far as reliability and reproducibility of the [oligonucleotide synthetic] method are concerned." This reference also discloses at p. 93, section (xv), that a di-protected adenosine derivative may be effectively dissolved in toluene prior to evaporative solvent removal for the purpose of co-evaporating residues of pyridine therefrom (see also p. 96, section (vi) for a similar disclosure). Additionally, at p. 111, section 7.6, the listing of solvents useful in oligonucleotide synthesis includes both benzene and toluene. This reference at the noted locations does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

The teachings of the prior art Caruthers '679 and Froehler '076 references motivate the selection of practically any organic solvent or

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solvent mixtures which will dissolve the reactants and not otherwise interfere with the intended synthetic transformation. The first three references (**A**, **G** and **H**) and the additional Caruthers et al. patents cited by Ravikumar et al.'621 provide descriptions of conventional
5 prior art processes for making oligonucleotides via phosphoramidite or H-phosphonate intermediates, including the 5'-O-deprotection process step and including details of how the process has been automated in **H** and by patents cited in **A**. The noted portions of the Caruthers '679 and Froehler '076 both teach that the choice of a
10 particular solvent or solvent mixture is a variable clearly within the purview of the ordinary practitioner. The Sproat et al.(I) (**W**), Conway et al., Atkinson et al., and Sproat et al.(II)(**RA**) references are each generally directed to oligonucleotide synthesis thereby providing proper motivation to combine with the primary references.
15 The secondary references provide disclosures that at least two different nucleoside-3'-O-phosphoramidites, at least one dinucleotide derivative, and some other nucleoside derivatives may be effectively dissolved in the aromatic hydrocarbon solvents benzene and/or toluene. These disclosures are deemed to provide factually specific
20 motivations for the ordinary practitioner conducting routine experimentation to substitute toluene, benzene, or their closely related aromatic solvent relatives as substitutes for at least a portion of the solvents typically used during the deprotection step in oligonucleotide synthesis. For these reasons the instant process claims are deemed
25 to be lacking in any patentable distinction in view of the noted prior art.

Therefore, the instant claimed oligonucleotide processes would have been obvious to one of ordinary skill in the art having the

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above cited references before him at the time the invention was made.

Applicant's arguments filed December 22, 2000 have been fully considered but they are not persuasive.

5 Applicant states that "[a]utomated oligonucleotide synthesis regimes are known in the art to require specific conditions of time, temperature, reagent and solvent at each deprotection and coupling step" but has failed to provide documentation to support this
10 assertion of fact or portions of said documentation which require that the ordinary practitioner not undertake routine experimentation to optimize the process being automatically executed. Applicant then proceeds to speculate concerning the negative aspects of
15 experimentation, alleging that "even a slight departure from the optimal conditions provided in published regimes can introduce reductions in yield ...[and product purity]," a parade of horrors which does not appear to be anything more than a straw man. Applicant then alleges that "practitioners in the art typically exercise great care not to deviate from standard automated synthetic
20 protocols," and again fails to provide any documentation to support this asserted reality wherein ordinary practitioners apparently avoid even thinking about optimizing the process via routine experimentation. Examiner remains skeptical of this view of automated oligonucleotide synthesis in light of the ongoing pressure of corporate business managers to minimize production costs, regardless
25 of the production process.

Applicant than argues at page 5, line 6 et seq that "[t]here is nothing in the art cited by the Office Action that would suggest the

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desirability of modifying the customary deprotection protocols use in automated oligonucleotide synthesis." Examiner notes that the rejection of record is under 35 U.S.C. §103(a) (obviousness), not 35 U.S.C. §102(b) (anticipation), and that applicant argument appears to
5 be incorrectly assuming the latter rather than the former standard.

Applicant then argues that the cited prior art fails to provide the requisite suggestion to motivate the ordinary practitioner. Examiner respectfully disagrees, noting repeated statements in more than one cited prior art reference to the effect that the ordinary
10 practitioner is free to select any solvent that works. That the companies marketing automated oligonucleotide synthesis apparatus have slavishly followed the first protocols that they elected to optimize does not mean that other protocols of equal or superior efficiency did not exist and could not be discovered by the ordinary
15 practitioner in the course of routine experimentation. Such routine experimentation is deemed to be within the scope of the cited prior art specifically because of the statements noted in the rejection supra which either fail to specify a required solvent or indicate that any solvent that works as a substitute for the solvents used in examples
20 are within the scope of the disclosure.

Applicant then argues that the "Office action identifies no "motivating force" that would have "impelled" persons of ordinary skill to modify the teachings of the cited prior art to arrive at Applicant's claimed invention." Examiner notes that the teachings of
25 the prior art are seen differently by different parties, and that Examiner's argument continues to be that the scope of the prior art disclosures is sufficiently broad to accommodate routine experimentation. Routine experimentation is deemed to include

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5 solvent substitution and therefore that, although not specifically described therein, applicant's claimed subject matter actually lies within the boundaries of the cited prior art because of the comments within the prior art to the effect that the choice of solvent is open to the practitioner.

10 Applicant then argues at length citing reports of the effect of reductions in yields on multistep processes, etc. that routine experimentation is "risky," because it might produce less optimal results. Advances in the art are produced by those ordinary practitioners who not deterred by such "risks" and who think that an equally good or better result is possible.

15 Applicant then argues that "none of these statements in the cited art are in the context of **automated oligonucleotide synthesis**", concluding that "the standard applied by the Office Action is *not* the appropriate standard for an obviousness determination." (emphasis in the originals). In light of amendments made to the grounds of rejection these quoted comments by applicant are not longer on point.

20 Applicant's conclusion that the instant claimed subject matter is not taught or suggested by the prior art is not found convincing and applicant's very narrow view of the metes and bounds of routine experimentation are also found to be far too narrow, particularly in view of the clear statements of the prior art which indicate that solvent choice is not a critical variable, a clear suggestion and teaching that the scope of the prior art includes solvents not specifically referred to therein. For these reasons, applicant's arguments are not found convincing and, the instant amended grounds of rejection are deemed to remain valid.

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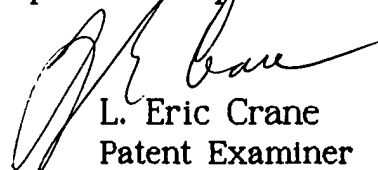
Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **703-308-4639**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Gary Geist, can be reached at (703)-308-1701.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **703-308-1235**.

LECrane:lec
04/03/01



L. Eric Crane
Patent Examiner
Group 1600